REMARKS

Claims 1-26 and 42 are pending in this application. Claims 19 and 26 have been canceled, and new claims 43-54 have been added. Claims 2-15, 18, 20, 23-25, and 42 have been amended to add the phrase "or pharmaceutically acceptable salt thereof". Claims 16 and 17 have been amended merely to modify the claim dependency. Claim 20 has been further amended to independent format, as well to recite particular disorders. Claim 21 has been further amended to preserve antecedent basis. Claims 1, 2, and 5 have been amended to replace the term "C_{1-8} alkenyl" with the term "C_{2-8} alkenyl". Claim 1 has been further amended to make the definition of R^3 even more clear, without narrowing the scope of the claim. Support for the new claims and amendments can be found throughout the original specification and claims, for example, in original claims 3, 4, 16 and 17 (new claims 51-54). No new matter has been added. Applicants further assert that the amendments to the claims do not narrow the scope of the claims.

After entry of this amendment, claims 1-18, 20-25, and 42-54 will be pending in this application.

The specification has been amended merely to clarify the priority claim as set forth in the Application Data Sheet filed with the present application and in the official filing receipt mailed on August 24, 2007. No new matter has been added.

I. Supplemental Information Disclosure Statement

Applicants will be filing a supplemental information disclosure statement within the next few days for consideration by the Examiner. Applicants thank the Examiner for her consideration of the previously submitted information disclosure statement.

II. The Claims Are Enabled

Claims 19, 20, and 23-25 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In particular, the Office alleges that the "terms 'disorders of the central nervous system, cardiovascular disorders and gastrointestinal disorders" covers a broad array of different disorders that have different modes of action and different

origins" (Office Action, page 2). The Office goes on to list several central nervous system disorders including AD, Parkinson's disease, Pick's disease, ALS, dementias, spinal muscular atrophies, spinocerebellar degenerations, and Huntington's disease, stating that "the great majority of these have no treatment at all" (Office Action, pages 3-4). Citing to AD, the Office alleges that there is "clear evidence that the skill level in this art is low relative to the difficulty of the task" (Office Action, page 4). The Office concludes that "[w]here utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of *in vivo* efficacy by those skill in the art" (Office Action, page 4).

As a preliminary matter, Applicants note that the Office appears to have acknowledged the enablement of the methods of treating **obesity** (claim 21) and **male erectile dysfunction** (claim 22), as these claims are not included in the listing of the rejected claims in section 1 of the Office Action (page 2). While Applicants disagree with the Office's conclusions regarding the enablement of the claimed methods, Applicants have canceled claim 19, solely to advance prosecution. Applicants have further amended claim 20 and added new claims 43-50. Applicants reserve the right to pursue the canceled subject matter in a future continuing application. Applicants respectfully assert that the methods of the amended and new claims are fully enabled for the reasons set forth below.

As will be recognized, the enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied

> on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling.
>
> ... it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Thus, any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974). Further, the proper standard for an enablement inquiry rests on whether one skilled in the art would be able to make and use the invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d at 1404. Factors for consideration in determining whether undue experimentation is necessary to make and use the invention include 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims.

Applicants respectfully assert that the Office has failed to provide any reasoning or evidence for why a person of skill in the art would not accept that the claimed compounds would work to treat the specific disorders of claim 20 or to decrease food intake, induce satiety, and control weight gain. Further, Applicants respectfully assert that the art clearly demonstrates that one skilled in the art would accept that a 5-HT_{2c} agonist, such as compounds of the present application, would be useful in the claimed disorders for the reasons summarized below.

A. Methods of decreasing food intake, inducing satiety, and controlling weight gain (claims 23-25)

The Office rejects claims 23-25, reciting methods of decreasing food intake inducing satiety, and controlling weight gain but fails to give any reason for why these methods are not enabled. Indeed, in its discussion of the enablement rejection, the Office Action is completely silent with regard to these particular methods. Hence, Applicants respectfully assert that the Office has failed to carry its burden under *In re Marzocchi* to provide evidence or reasoning to back up its assertions of non-enablement. Accordingly, the burden has not shifted to Applicants to provide rebuttal evidence to show the enablement of the claimed methods.

Nonetheless, Applicants respectfully note that the art clearly demonstrates that one skilled in the art would accept that compounds of the present application can decrease food intake, induce satiety, and control weight gain of a mammal without having to engage in undue experimentation. Compounds of the present application have been shown to be agonists of the 5-HT_{2c} receptor in an IP accumulation assay (see specification, Example 29, page 48, lines 11-22). Further, 5-HT_{2c} agonists have been shown to increase satiety and induce undereating in animal studies, while 5-HT_{2c} knock-out mice have been shown to be hyperphagic and unresponsive to the anorectic effects of 5-HT_{2c} agonists (see e.g., Bickerdike, "5-HT_{2c} receptor agonists as potential drugs for the treatment of obesity", *Current Topics in Medicinal Chemistry*, 3:885-897 (2003), "Bickerdike"; and Tecott, et al., "Eating disorder and epilepsy in mice lacking 5-HT_{2c} serotonin receptors", *Nature*, 374:542-546 (1996)). Further, administration of mCPP, a 5-HT_{2c} agonist, to human obese subjects resulted in significant weight loss (Bickerdike, page 892). Hence, one skill in the art would accept that 5-HT_{2c} agonists, such as the compounds of claim 1, would be useful to decrease food intake, induce satiety, and control weight gain as recited by the claimed methods without engaging in undue experimentation. Accordingly, Applicants respectfully assert that the methods of claims 23-25 are fully enabled and request that the claim rejections be withdrawn.

B. Methods of treating depression, atypical depression, anxiety, obsessive-compulsive disorder, social phobia, panic states, sexual dysfunction, psychoses, schizophrenia, and epilepsy (amended claim 20 and new claims 43-49)

As noted above, Applicants have canceled claim 19 and amended claim 20 to recite particular disorders. The Office fails to provide any reason for why the particular treatment methods of amended claim 20 are not enabled.[1] While the Office Action briefly mentions epilepsy in a laundry list of central nervous system disorders, the Office fails to give any specific reason for the alleged lack of enablement of this particular disorder. Further, in its discussion of the enablement rejection, the Office Action is completely silent to the remaining disorders in amended claim 20.[1] Hence, Applicants respectfully assert that the Office has failed to carry its burden under *In re Marzocchi* to provide evidence or reasoning to back up its assertions of non-enablement. Accordingly, the burden has not shifted to Applicants to provide rebuttal evidence to show the enablement of the claimed methods.

Nonetheless, Applicants respectfully note that the art clearly demonstrates that one skilled in the art would accept that a 5-HT_{2c} agonist can treat the disorders recited by amended claim 20, without having to engage in undue experimentation. *See e.g.,* Tecott, et al., "Eating Disorder and Epilepsy in Mice Lacking 5-HT_{2c} Serotonin Receptors", *Nature*, 374:542-546 (1996) (epilepsy-5-HT_{2c} knock-out mice subject to death from seizures); Isaac, "The 5-HT_{2C} receptor as a potential therapeutic target for the design of antiobesity and antiepileptic drugs" *Drugs of the Future* (2001), 26(4), 383-393 (epilepsy); Jenck, et al., "Antiaversive effects of HT_{2c} receptor agonists and fluoxetine in a model of panic-like anxiety in rats", *European Neuropsychopharmacology*, 8:161-168 (1998) (social phobias, panic disorders); Millan, et al., "HT_{2c} Receptors Mediate Penile Erections in Rats: Actions of Novel and Selective Agonists and Antagonists", *Eur. J. Pharmacol.* 325:9-12 (1997) (sexual dysfunction); Martin et al. "5-HT_{2C} receptor agonists pharmacological characteristics and therapeutic potential", *Journal of Pharmacology and Experimental Therapeutics* (1998), 286(2), 913-924 (sexual dysfunction-eliction of penile erections, obsessive-compulsive disorder-reduction in compulsive burying and schedule-inducted polydipsia in rats and compulsive scratching in squirrel monkeys); Bos et al., "Novel Agonists of 5HT_{2C} Receptors. Synthesis and Biological Evaluation of Substituted 2-{Indol-1-yl)-1-methylethylamines and 2-(Indeno[1,2-b]pyrrol-1-yl)-1-methylethylamines.

[1] In section 2, the Office separately addresses the enablement of drug and alcohol addiction. Applicants address this portion of the rejection in section II.C of this response.

Improved Therapeutics for Obsessive Compulsive Disorder, *Journal of Medicinal Chemistry* (1997), 40(17), 2762-2769 (obsessive-compulsive disorder-reduction in schedule-induced polydipsia in rats); Chahal, *ThomsonPharma, Literature and News Report*, May 17-18, 2000 (depression); Piesla et al., "Atypical Antipsychotic-like Effects of 5-HT_{2c} Agonists", *Abstracts of the 8th International Congress on Schizophrenia Research. British Columbia*, Canada, (April 28-May 2, 2001), Schizophrenia Research 49:95 (col. 2) (psychoses, schizophrenia); Clinical trial NCT00768612, "Study Evaluating Safety and Tolerability of Vabicaserin in Patients With Sudden Worsening of Schizophrenia Study", *http://clinicaltrials.gov/ct2/show/record /NCT00768612* (planned clinical trial for vabicaserin, 5-HT_{2C} agonist, for schizophrenia); and Rosenzweig-Lipson, et al., "Vabicaserin: effects of a novel 5HT2C agonist on medial prefrontal cortex neurotransmission, cognition and sensorimotor gating", *20th ECNP Congress*, Vienna, Austria (2007) (psychoses, schizophrenia). Accordingly, Applicants respectfully assert that the methods of claims 20 are fully enabled and request that the claim rejections be withdrawn.

C. Methods of treating drug and alcohol dependence (amended claim 20 and new claim 50)

Claim 20 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement with respect to "diagnosis, treatment, prevention, or alleviation...drug and alcohol addiction" (Office Action, page 5). The Office alleges that there "is not, and probably never will be a pharmacological treatment for 'drug addiction' generally" (Office Action, page 5). The Office asserts that alcohol and various drug addictions arise from involvement of different receptors and that, therefore, "[a]ll attempts to find a pharmaceutical to treat chemical addictions generally have thus failed" (Office Action, page 5).

Applicants respectfully assert that these conclusory statements do not carry the Office's burden to provide evidence or reasoning to back up its assertions of non-enablement as required by *In re Marzocchi*. The Office has cited no evidence of the supposed complete lack of treatments available for chemical addictions. Indeed, the record before the Office clearly shows that 5-HT_{2c} agonists have been shown to reduce cocaine, nicotine, and alcohol self-

administration in animal studies (see e.g., Higgins, et al. "Serontonin and drug reward: focus on 5-HT_{2c} receptors", *European J. of Pharmacology*, (2003), 480:151-162, at page 155-156). Accordingly, Applicants respectfully assert that methods of treating drug and alcohol addiction are fully enabled and request that the claim rejections be withdrawn.

III. The Claims Are Definite

Claims 1-5, 16-26, and 42 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite as summarized in paragraphs (a) to (i) in section 3 of the Office Action. In paragraph (a), the Office alleges that "C_1 alkenyl" is vague and indefinite as an alkenyl group must contain two carbon atoms. Claims 1, 2, and 5 have been amended to replace the term "C_{1-8} alkenyl" with the term "C_{2-8} alkenyl", thereby rendering the rejection moot.

In paragraphs (b) to (e), the Office alleges that "7-benzyloxy", "7-(1-phenyl-ethoxy)", "7-phenethyloxy", and "7-(3-phenyl-propoxy)" in claim 16 lack antecedent basis from claim 2. Applicants have amended claim 16 to dependent from claim 1, thereby rendering the rejection moot.

In paragraph (f), the Office alleges that the species (a) to (k) in claim 16 lack antecedent basis from claims 3 and 4. Applicants respectfully assert that one of skill in the art would recognize that the methyl group at the R^2 position of each species in claim 16 can be in the (S)- or (R)-conformation as in claims 3 and 4. Hence, Applicants respectfully assert that claim 16 does not lack antecedent basis from claims 3 and 4. However, solely to advance prosecution, Applicants have amended claim 16 to depend from claim 1 and have added new claims 51 and 52 reciting the (R)- and (S)-enantiomers of the compounds of claim 16, thereby rendering the rejection moot.

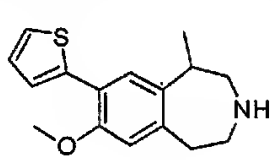
In paragraphs (g) to (j), the Office alleges that "7-benzyloxy", "7-methoxy", "8-pyridin-3-yl", and "8-pyridin-2-yl" in claim 17 lack antecedent basis from claim 2. Applicants have amended claim 17 to dependent from claim 1, thereby rendering the rejection moot.

In paragraph (k), the Office alleges that the species (a) to (l) in claim 17 lack antecedent basis from claims 3 and 4. Applicants respectfully assert that one of skill in the art would

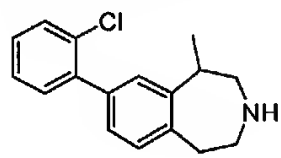
recognize that the methyl group at the R^2 position of each species in claim 17 can be in the (S)- or (R)-conformation as in claims 3 and 4. Hence, Applicants respectfully assert that claim 17 does not lack antecedent basis from claims 3 and 4. However, solely to advance prosecution, Applicants have amended claim 17 to depend from claim 1 and have added new claims 53 and 54 reciting the (R)- and (S)-enantiomers of the compounds of claim 17, thereby rendering the rejection moot.

IV. The Claims Are Novel

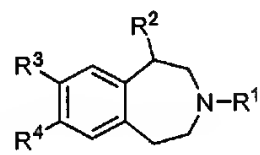
Claims 1-4, 11, 13, 18-21, 23-26, and 42 are rejected as allegedly lacking novelty over U.S. Patent No. 6,953,787 ("Smith"). In particular, the Office points to Examples 15 and 48. Applicants respectfully assert that claim 1, and dependent claims thereof, are novel over Examples 15 and 48 of Smith (shown below, along with Formula (I) of the present application). Examples 15 and 48 do not fall within the scope of claim 1, due to proviso (c) and (d). Proviso (c) provides that when R^1 is H, R^2 is CH_3, R^3 is 2-chlorophenyl, then R^4 is other than H. Hence, proviso (c) clearly excludes Example 48. Similarly, proviso (d) provides that when R^1 is H, R^2 is CH_3, R^3 is 2-thienyl, then R^4 is other than methoxy. Hence, proviso (d) clearly eliminates Example 15. Accordingly, Applicants respectfully assert that the claims are novel over claim 1, and dependent claims thereof, and request that the claim rejections be withdrawn.



Example 15



Example 48



(I)

V. Obviousness-Type Double Patenting

Claims 1-6, 10, 13-21, 23-26, and 42 are rejected on the grounds of non-statutory obviousness-type double patenting over claims 1, 3-6, 12, 15, 17-23, 25, and 77 of U.S. Patent No. 6,953,787. Applicants will file a terminal disclaimer if appropriate upon an indication of

allowable subject matter. Accordingly, Applicants respectfully request that the rejection be held in abeyance until the scope of the allowable subject matter becomes clear.

Claims 19-21 and 23-26 are provisionally rejected on the grounds of non-statutory obviousness-type double patenting over claims 1, 13-18, 21, 22, 31-43, 46, 47, 58-63, 66, 67, 73, and 75 of application serial no. 10/917,979. As the rejection is provisional in nature, Applicants will determine whether a terminal disclaimer is appropriate upon an indication of allowable subject matter.

Claims 1-6, 9-11, and 13-26 are provisionally rejected on the grounds of non-statutory obviousness-type double patenting over claims 1-3, 5-7, and 9-12 of application serial no. 11/599,050. As the rejection is provisional in nature, Applicants will determine whether a terminal disclaimer is appropriate upon an indication of allowable subject matter.

Claims 1-26 are provisionally rejected on the grounds of non-statutory obviousness-type double patenting over claims 47-50, 52-55, and 58-65 of application serial no. 11/560,953. As the rejection is provisional in nature, Applicants will determine whether a terminal disclaimer is appropriate upon an indication of allowable subject matter.

Claims 1-26 and 42 are provisionally rejected on the grounds of non-statutory obviousness-type double patenting over claims 1, 2, 4-11, 13, 16, 17, 19-32, and 48 of application serial no. 10/576,849. As the rejection is provisional in nature, Applicants will determine whether a terminal disclaimer is appropriate upon an indication of allowable subject matter.

VI. Conclusion

Applicants respectfully request reconsideration of the rejections of record and an indication of allowable subject matter. The Examiner is urged to contact Applicant's undersigned representative at (302) 778-8411 if there are any questions regarding the claimed invention.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050. Further, if not accompanied by an independent petition, this

paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline if necessary and authorizes the Commissioner to debit the petition fee and any other fees or credit any overpayment to Deposit Account No. 06-1050.

Respectfully submitted,

Date: March 2, 2009

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